REMARKS

Status of the Claims

Claims 1, 2, 5-30, 32, 34-38, 40 and 41 are pending in this application. Claim 33 has been canceled. No claims have been added. Claim 1 has been amended to recite that a thin-layer chromatography plate is used as the stationary phase and that the stationary phase is suitable for sequential chemical synthesis. Claim 1 has also been amended to recite that the compounds are separated by using a mobile phase. No new matter has been added by the above claim amendments.

Rejection under 35 USC 103(a)

The Examiner rejects claims 1, 2, 5-12, 15-30 and 33-36 as obvious over Mehta et al. USP 6,306,590 in view of Frank, *Spot Synthesis*. Applicant traverses the rejection and respectfully requests the withdrawal thereof.

The present invention is directed to a method for the sequential synthesis, separation and direct screening of compounds in the same bulk of a stationary phase on a thin layer chromatography (TLC) plate. The method offers a large degree of flexibility, most importantly with respect to the number of reactions, which can be performed in the same bulk of a stationary phase, but also with respect to techniques used for separation of the products.

Mehta '590 generally discloses a "multiphasic microfluidic apparatus" where synthesis and separation of the components occur in separate, albeit communicating compartments. The components are typically made or purified in the first phase and separated in the second phase. The Mehta apparatus is used in a polymerase chain reaction. The products generated in the PCR reaction are not *de novo* products, but instead are replications of known sequences. In a PCR reaction, the known sequence has a known isoelectric point. Since the products of the PCR have known isoelectric points, the identification and separation steps are not as relevant in comparison to identification and separation steps in the present invention where de novo product synthesis occurs. This is a fundamental difference with clear implications when it comes to the separating and screening steps.

Furthermore, Mehta teaches the use of gel electrophoresis for the separation technique. Gel electrophoresis is performed on a polyacrylamide bulk phase. On the other hand, in the present invention, the synthesis, separation and screening steps are all performed on a TLC plate. The two-dimensionality of the TLC provides for a number of advantages over gel electrophoresis, such as accessibility to the separated compounds for the next reaction step and *in situ* screening of the compounds.

Electrophoretic separation, in Mehta, involves a serious limitation not pertinent to eluent chromatography, namely the need

for allowing appropriate time for the separation. While this is practical in situations where a reference, such as the PCR template, may be used, separation of a variety of components of unknown physicochemical properties by electrophoresis may be seriously compromised by loss of one or more components due to migration out of the area available for subsequent assaying (such as migration into and degradation at the electrode or its immediate surrounding).

In Mehta, during synthesis, in gel electrophoresis, the reagents, compounds and substrates are confined and sealed off at each stage of the assay. Synthesis is confined to channels, and the reaction components are introduced through ports. See Mehta at col. 8, lines 42-48 "... *devices of the invention ...are substantially sealed to the outside environment, excepting reagent, buffer* or sample ports" and col. 5, line 66, which states that "*the* microfluidic phases of the invention typically comprise ... channels, chambers, wells or the like." Thus, the closed systems in Mehta do not allow for the liquid or fluid in the sealed area be replaced for subsequent uses.

Conversely, the use of thin-layer chromatography does not seal the reaction step to further reaction components to be added subsequently, i.e. suitable for sequential chemical reactions. Thus, the synthesis of different compounds or compound mixtures at distinct areas (spots) of the bulk (plate) by intentional

application of different reagents, substrates, or solvents, or mixtures thereof, to distinct areas of the plate are possible.

These advantages in the present invention are made possible by the open, accessible plate, which may be handled without any reagent, compound, or substrate being confined and sealed off at any point of the performance of the method.

Moreover, the method of Mehta requires pre-mixing all of the necessary components for the reaction and delivering the entire reaction mixture into the channel by pumping the mixture into the channel. Conversely, no pumping means is required in the present invention.

Applicant submits that the method of the present invention is performed on a different stationary phase than Mehta, for a different purpose than Mehta, and allows for sequential reactions to take place within the same spot. On the other hand, the method according to Mehta does not allow for sequential reactions to take place.

Although Mehta mentions the use of making a chemical library and mentions the use of TLC, none of the teachings of Mehta allow for the preparation of a chemical library obtainable from sequential reaction sequences and for the separation of products in the same bulk stationary phase by biological or biochemical methods.

Contrary to the Examiner's comments, Applicant notes that in Example 2 in Mehta, the reaction temperatures in the PCR are such that the methylcellulose would not solidify and thus, would result in a fluid bulk phase as opposed to a solid bulk phase, TLC plate, in the present invention.

The secondary reference Frank fails to disclose or suggest the separation of products on a stationary phase. Frank merely discloses performing reactions on a cellulose-based support and requires an anchoring process in the synthetic and screening process.

Applicant submits that if one of ordinary skill in the art were to combine the teachings of Mehta and Frank, one would have to first select a bulk phase, which allows for both synthetic chemistry and biological/biochemical screening methods. The bulk phase could not be one from either of Mehta and Frank because neither allows for the concept of sequential reaction processes. Mehta would have to be modified to synthesize de novo products, rather than mere replication of a known nucleic acid sequence.

Moreover, Applicant submits that the combination of references leads to several teachings away from the present invention. For example, the concept of anchoring in Frank is contrary to the present invention. The closed system in Mehta is also contrary to the present invention. Frank is deficient in that it fails to suggest that the bulk phase is good for a sequential separation

step and Mehta is deficient in that it fails to disclose or suggest screening in the same spot on the bulk phase.

Applicant submits that the Examiner is using impermissible hindsight to reconstruct the present invention. The Examiner merely relies on Applicants' own teachings to form the obviousness rejection. The Examiner has taken the instant invention and divided it into two parts. The Examiner has found each part in a separate reference. However, neither reference suggests combining the two to arrive at the instant invention. Such hindsight reconstruction is impermissible according to MPEP 2141 and In re Deminski, 796 F.2d 436, 443 230 USPQ 313, 316 (Fed. Cir. 1986).

In short, Mehta and Frank individually disclose components of the present invention. However, each of them accomplishes portions of the method of the invention by highly complex processes, and are thus highly limited in their utility and applicability. The inventiveness of the present invention lies, at least in part, in performing, in an effective manner, each of the steps in a singular medium through a simple and reliable technology.

Inasmuch as the combination of Mehta and Frank fail to suggest the combination of the references, Applicant submits that the present invention is not obvious over the cited references and the rejection should be withdrawn.

The Examiner also rejects claims 13 and 14 as obvious over Mehta in view of Frank and further in view of Hudak USP 6,034,361.

Applicant submits that this rejection also fails for the same reasons expressed above regarding the deficiencies in the combination of Mehta and Frank, since Hudak fails to compensate for those deficiencies. As such, this rejection should also be withdrawn.

The Examiner also rejects claims 37 and 38 as obvious over Mehta in view of Frank and further in view of Bataillard USP 5,482,372. Applicant submits that this rejection also fails for the same reasons expressed above regarding the deficiencies in the combination of Mehta and Frank, since Bataillard fails to compensate for those deficiencies. As such, this rejection should also be withdrawn.

The Examiner also rejects claims 40 and 41 as obvious over Mehta in view of Frank and further in view of DE 3,701,833 to Wolfbeis. Applicant submits that this rejection also fails for the same reasons expressed above regarding the deficiencies in the combination of Mehta and Frank, since DE '833 fails to compensate for those deficiencies. As such, this rejection should also be withdrawn.

Conclusion

As Applicant has addressed and overcome all rejections in the Office Action, Applicant respectfully requests that the rejections be withdrawn and that the claims be allowed.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petition(s) for a one (1) month extension of time for filing a reply in connection with the present application, and the required fee of $110.00 is attached hereto.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Kecia Reynolds (Reg. No. 47,021) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____ (Reg. No. 24,046)
for Gerald M. Murphy, Jr., #28,977

GMM/KJR/crt
0459-0490P

P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000